

Rapidly fatal encephalitis associated with atypical lymphoid proliferations of the basal ganglia subsequent to aneurysmal subarachnoid hemorrhage

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Abstract

Rapidly fatal encephalitis associated with atypical lymphoid proliferations after intracranial aneurysm rupture has not been reported. Here, we describe a 52-year-old female who presented to the emergency department with a severe headache. Imaging demonstrated aneurysmal subarachnoid hemorrhage due to a ruptured left posterior inferior cerebellar artery aneurysm, which was treated with endovascular embolization and subsequent external ventricular drain. She recovered without neurologic sequelae by day seven; however, five weeks later she represented with a severe headache associated with nausea and fever. Initial repeat imaging was unremarkable. She deteriorated quickly and was empirically treated for meningitis despite negative cerebrospinal fluid studies. Magnetic resonance imaging revealed diffuse cerebral edema within the basal ganglia and thalamus. Biopsy of the caudate nuclei revealed atypical lymphoid proliferations. She was treated accordingly with no significant improvement. This case highlights the necessity for a better understanding of the etiology, chronology, and natural history of atypical lymphoid proliferations.

Introduction

Traditionally, lymphoid proliferations have been classified as benign or malignant processes, such as reactive hyperplastic or lymphoma, respectively.¹ However, there are cases where lymphoid lesions are biologically indeterminate where the tissue may exhibit histopathologic characteristics suggestive of a malignant process but can-

not be diagnosed as such based upon specified criteria. In this instance, a diagnosis of atypical lymphoid proliferations may be given, which serves as a grey zone between benign and malignant lymphoid proliferations. Nonetheless, atypical lymphoid proliferations are not always premalignant and may signify a benign lesion imitating a malignant process. Typically, atypical lymphoid proliferations are associated with specific viral infections, such as Epstein-Barr virus, autoimmune disorders, immunodeficiencies, or specific medications. Progression and timeline of these conditions are variable; however, rapidly fatal cases are uncommon. Here, we describe a case of a rapidly progressive and fatal encephalitis associated with atypical lymphoid proliferations of the basal ganglia in a patient recently treated for a ruptured posterior inferior cerebellar artery aneurysm.

Case Report

A 52-year-old female presented to the emergency department with nausea, vomiting, and a severe headache. Computed tomography (CT) demonstrated subarachnoid hemorrhage anterolateral to the medulla. Cerebral diagnostic angiogram revealed a left posterior inferior cerebellar artery aneurysm (Figure 1A and B). The aneurysm was treated with endovascular embolization but complicated by intraoperative rupture necessitating placement of an external ventricular drain (Figure 1C and D). Routine cerebrospinal fluid samples were without evidence of infection. The external ventricular drain was removed on post-procedure day six. On post-procedure day seven, she was neurologically intact without evidence of sequelae. She was seen in clinic three weeks after her initial presentation to the emergency department. At that time, she was neurologically intact without complaints.

She presented again to our emergency department two weeks later (five weeks after her initial presentation) with nausea, vomiting, fever, hypotension, and a severe headache. Repeat CT was without evidence of hemorrhage (Figure 2A). A lumbar puncture was performed, which revealed a leukocytosis with a neutrophilic predominance. Although cerebrospinal fluid gram stain and cultures remained negative, intravenous vancomycin, cefepime, and acyclovir were started for presumed external ventricular drain-related meningitis. The following day she was transferred to the intensive care unit for respiratory failure, seizure activity, and decerebrate posturing. Electroencephalography was without evi-

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dence of epileptiform activity. Magnetic resonance imaging (MRI) fluid-attenuated inversion recovery (FLAIR) sequence on hospital day three demonstrated significant cerebral edema within the basal ganglia, thalamus, hippocampus, midbrain, and pons without evidence of diffusion restriction or contrast enhancement (Figure 2B). Repeat MRI FLAIR on hospital day 10 demonstrated exacerbation of the edematous process (Figure 2C).

Without a diagnosis to guide treatment, a brain biopsy was planned. A stereotactic-guided biopsy of the right caudate was performed. Microscopic examination revealed infiltration of small vessels with a mixture of small and larger atypical appearing lymphoid cells, with some of the large atypical cells exhibiting parenchymal infiltration (Figure 3A and B). Immunostaining demonstrated large atypical cells immunoreactive for CD20 suggesting a B-cell population with CD3 reactive T-cells intermixed with the atypical B-cell population (Figure 3C and D). *In situ* hybridization assays demonstrated a larger number of atypical cells expressing lambda light chain with a small number of cells expressing kappa light chain (Figure 3E and F). Final diagnosis of the biopsy specimen was consistent with

atypical lymphoid proliferations of the caudate. The patient was started on intravenous immunoglobulin and intravenous steroids for immune-mediated pathology without clinical improvement. Workup for bacterial, fungal, and viral causes including Epstein-Barr, influenza, parainfluenza, herpes simplex, varicella-zoster, western equine encephalitis, eastern equine encephalitis, St. Louis encephalitis, California encephalitis, West Nile virus and rhinovirus were unremarkable. The patient's cefepime was discontinued as a possible source of cephalosporin encephalopathy without clinical improvement.² The patient expired on hospital day 23 (approximately eight weeks from initial presentation).

Discussion

Rupture of an intracranial aneurysm is associated with significant morbidity and mortality.³ In patients being treated for ruptured intracranial aneurysms, intra-procedural rupture during endovascular coiling of an aneurysm carry a peri-procedural death or disability of up to 63%.⁴ In addition, for patients who do survive, postsurgical and post-procedural sequelae are common. Common reasons for a patient to exhibit delayed mental status deterioration can include re-rupture, vasospasm, hydrocephalus, seizures or infection.⁵ However, catastrophic and irreversible deterioration five weeks after rupture is exceedingly uncommon. The initial workup should include imaging (CT and MRI) as well as diagnostic cerebral angiogram to rule out hemorrhage, infection, vasculitis, and delayed vasospasm. The findings of atypical lymphoid proliferations on biopsy yield a pathological entity that is not common in neurosurgical patients.

Atypical lymphoid proliferations can be associated with benign and self-limited processes, or malignant and potentially fatal diseases. The cells may represent a response to stress or be a precursor to lymphoma. Atypical lymphoid proliferations are the result of a polyclonal immune response to antigenic stimulation.¹ The causes are often broken down into one of five categories: infectious, immunodeficiency, medication-associated, immunosuppressive drugs, and autoimmune diseases.⁶ Much of the literature surrounding central nervous system atypical lymphoproliferative diseases are found in immunocompromised patients, such as those with solid organ transplants necessitating immunosuppressant regimens with subsequent activation of the Epstein-Barr virus leading to lymphoid proliferation or hyperplasia.^{3,5,7,8} Epstein-Barr virus

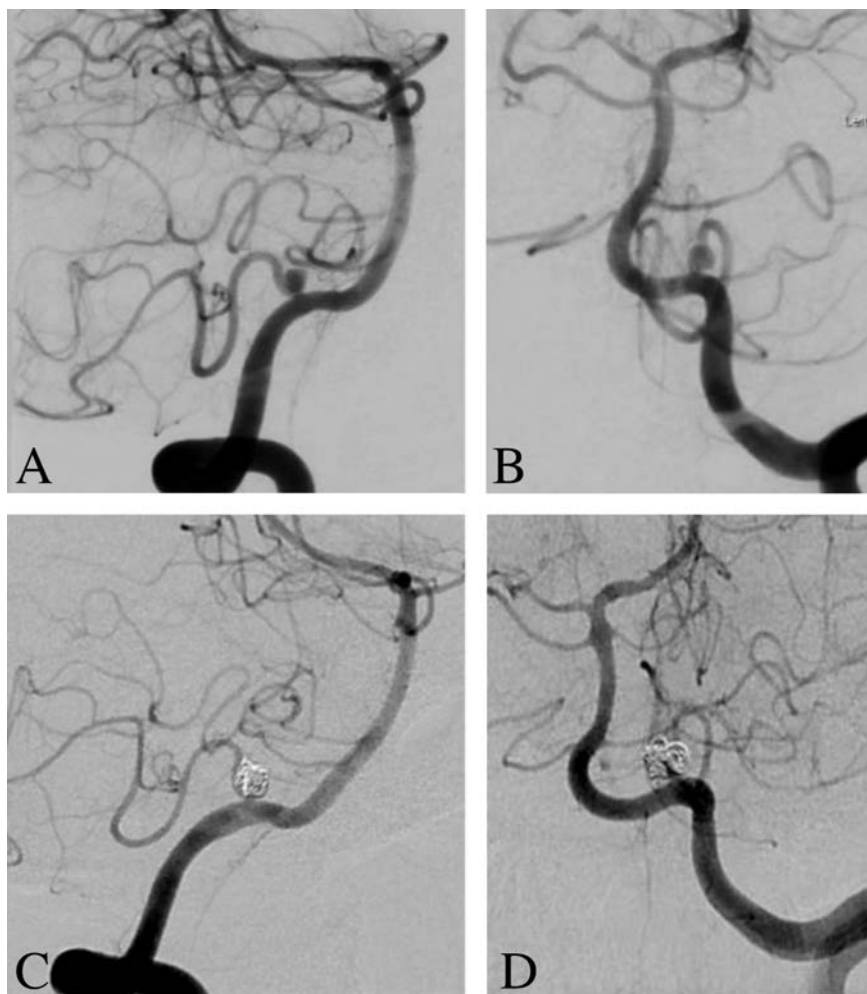


Figure 1. Cerebral angiography pre- and post-embolization of a left posterior interior cerebellar artery aneurysm. A-B) Lateral and anteroposterior cerebral angiogram demonstrates a left posterior interior cerebellar artery aneurysm pre-embolization. C-D) Lateral and anteroposterior cerebral angiogram demonstrating coil embolization of the posterior interior cerebellar artery aneurysm with preservation of the parent vessel and mild vasospasm.

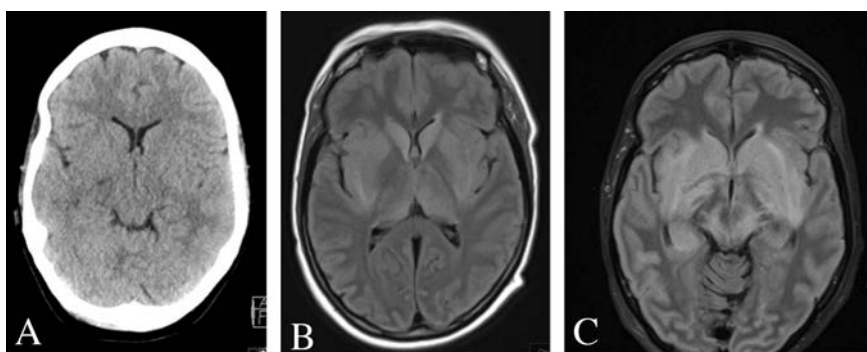


Figure 2. Imaging on readmission. A) CT head without acute pathology on day of readmission. B) MRI Fluid-Attenuated Inversion Recovery (FLAIR) sequence on hospital day three demonstrating significant hyperintensities within the bilateral caudate nuclei, putamen, claustrum, internal capsule, external capsule, extreme capsule, amygdala, hippocampus, thalamus, midbrain and pons without evidence of diffusion restriction or contrast enhancement. C) Repeat MRI FLAIR on hospital day 10 showing significant exacerbation of the edematous process.

seropositivity is found in greater than 90% of people worldwide.⁹ Epstein-Barr virus DNA quantitative polymerase chain reaction was negative in our patient, which is thought to have a sensitivity on 94.9% and a specificity of 97.4% in primary Epstein-Barr virus infections.¹⁰

Although there is currently no known direct correlate between aneurysmal subarachnoid hemorrhage and the inception of an atypical lymphoid proliferation, we postulate that an exacerbation of an inflammatory response within the subarachnoid space may be a culprit. It is known that rupture of an intracranial aneurysm and consequential subarachnoid hemorrhage results in diffuse systemic pathology and, importantly, appears to modulate immunobiology.¹¹⁻¹⁴ Moreover, there is evidence to suggest that the products of erythrocyte degradation within the subarachnoid space ultimately initiate an inflammatory cascade as well as a state of relative immunodepression.¹¹⁻¹⁴ Indeed, intracranial aneurysmal rupture is unlikely to directly cause the inception of a malignant process such as atypical lymphoid proliferations of the basal ganglia described herein. However, we hypothesize that consequences of uncontrolled neuroinflammation and resultant immunodepres-

sion from aneurysmal rupture may have allowed a pre-existing atypical lymphoid proliferation to undergo aggressive expansion as depicted in the present case.

As Greiner *et al.*⁶ describe, management considerations of atypical lymphoid proliferations depend on the etiology of the lymphoid proliferation. Identification of the causative factors is paramount to effective treatment. Identification and cessation of offending medications need to be considered. Medications such as immunosuppressants, phenytoin, and non-steroidal anti-inflammatory drugs can be implicated. While phenytoin has been implicated in atypical lymphoid proliferations, our patient had been treated with levetiracetam. The use of acyclovir may reduce viral replication and be useful in herpes virus infections or active Epstein-Barr virus infections, as well as coverage for other possible etiologies of viral meningitis. Though our patient did not display any syndromic or clinical features of autoimmune diseases (*i.e.*, rheumatoid arthritis, Sjogren's syndrome or systemic lupus erythematosus) or a primary immunodeficiency (X-linked lymphoproliferative disease, Wiskott-Aldrich syndrome, severe combined immunodeficiency), these disorders need to

be considered in the differential diagnosis. Importantly, when faced with the diagnosis of atypical lymphoid proliferations, the physician should use all available resources to differentiate and define the lymphoid proliferation as specifically as possible in an attempt to establish whether the proliferation is benign or malignant. Some resources include immunohistochemical, molecular studies, utilizing expert opinions, and re-biopsy.⁷

Conclusions

Mortality of a ruptured aneurysm approaches 50%,³ with each rupture leading to a more dismal prognosis.⁴ Postoperative complications are not uncommon, though most will occur within the first two weeks.¹⁵ This is the first case, to our knowledge, of a rapidly fatal encephalitis post-aneurysmal rupture associated with atypical lymphoid proliferations of the brain parenchyma. Because atypical lymphoid proliferations exist as an amorphous designation in histopathology, the diagnosis and treatment strategies vary widely. This case highlights the need for a better understanding of the

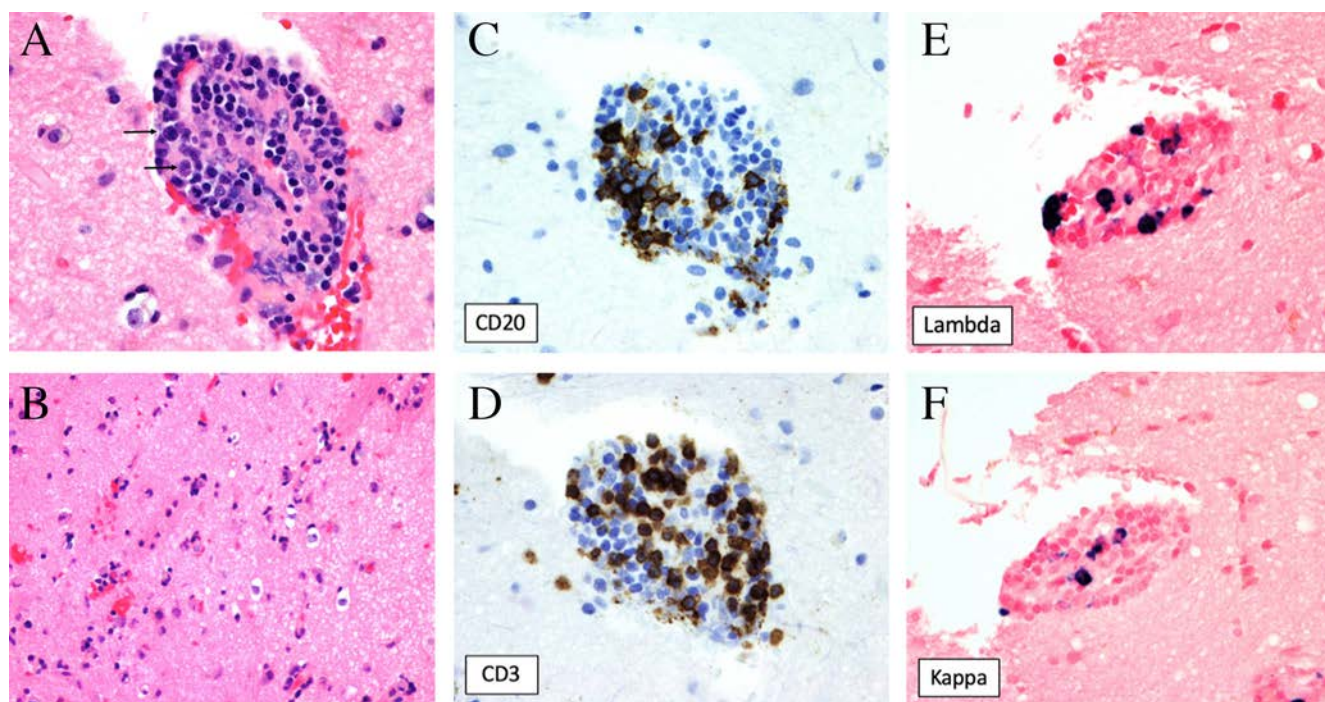


Figure 3. Histopathology from biopsy of the right caudate. A) Intraparenchymal vessels with perivascular inflammatory cells varying from small lymphocytes to larger, pleomorphic cells (arrows) ($\times 10$). B) Sections of the basal ganglia biopsy displaying mild gliosis and inflammatory infiltrates ($\times 40$). C) Immunostaining demonstrated large atypical cells immunoreactive for CD20 suggesting a B-cell population ($\times 40$). D) Immunostaining demonstrated CD3 reactive T-cells intermixed with the atypical B-cells population ($\times 40$). E-F) *In situ* hybridization assays demonstrated a larger number of atypical cells expressing lambda light chain with a small number of cells expressing kappa light chain ($\times 40$).

patterns of atypical lymphoid proliferations etiology, chronology, and mortality. In particular, clarification of early signs and symptoms are needed in order to allow clinicians to obtain a timely diagnosis and provide appropriate treatment to prevent rapid and fatal progression.

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